JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

New liver–β-cell axis that controls insulin secretory capacity

Glucose production by the liver is a major physiological function, required to prevent the development of hypoglycemia in postprandial and fasted states. Hepatic glucose metabolism is highly regulated not only by changes in plasma insulin and glucagon levels, but also by changes in blood glucose concentrations. In the fasted state, a decrease in glycemia reduces the intracellular levels of glucose and glucose-6-phosphate, thereby favoring glycogen degradation. The last steps of glucose secretion involve the diffusion of glucose out of the endoplasmic reticulum (ER) and into the cytosol followed by its release from the hepatocytes by a facilitated diffusion mechanism through glucose transporter 2 (GLUT2). GLUT2 is a facilitative glucose transporter located in the plasma membrane of the liver, pancreas, intestine, kidney and brain. Because of its low affinity and high capacity, GLUT2 ensures large bidirectional fluxes of glucose in and out of the cell.

In previous studies, it has been shown that the absence of GLUT2 suppresses glucose uptake and facilitates glucose diffusion across the hepatocyte plasma membrane; however, in the fasted state, the hepatic glucose secretion was normal[1,2]. Furthermore, it provided evidence that this process takes place through a membrane traffic-based mechanism. Thus, in the fasted state, hepatic glucose release does not require the presence of GLUT2 or any plasma membrane facilitated diffusion glucose transport mechanism. This implies the existence of a new pathway for glucose release, which might be based on a membrane traffic mechanism. However, these conclusions were obtained by studying mice with a constitutive and systemic deletion of the GLUT2 gene. Therefore, the possible activation of an unphysiological compensatory pathway could not be excluded.

In a recent article, Seyer *et al.*[3] investigated the physiology of adult mice with an induced liver-specific inactivation of the GLUT2 gene. Their experiments show that the inactivation of GLUT2 suppressed glucose uptake by hepatocytes, but had no effect on the hepatic glucose secretion and homeostasis in the fed and fasted states.

That important study showed that hepatic glucose uptake depends on GLUT2 expression, but the presence of this transporter does not affect the normal glycemic control during the postprandial state and the rate of hepatic glucose production in the fasted sate. However, during fasting, GLUT2 is required for the equilibration of cytosolic glucose with the external space to allow normal glycogen mobilization, and suppression of glycolytic and lipogenic gene expression; processes that are activated by elevated glucose levels.

Despite the lack of an acute effect of hepatic GLUT2 inactivation on glucose homeostasis, long-term observations showed that the deregulation of liver glucose metabolism leads to the progressive

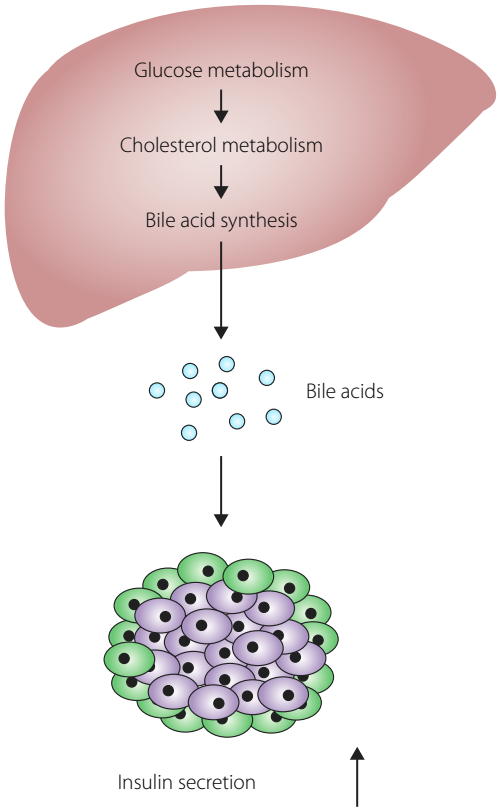

Figure 1 | Hepatic glucose sensing controls β-cell glucose competence through the regulation of bile acid production. The absence of glucose transporter 2 in the liver is associated with a coordinated downregulation of the cholesterol biosynthesis genes leading to lower bile acid production. This leads to a progressive development of glucose intolerance as a result of a reduced insulin secretory capacity in β-cells. Bile acids might constitute a link between hepatic glucose sensing and the preservation of β-cell glucose competence.

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Received 19 December 2013; accepted 24 December 2013

development of glucose intolerance. This was as a result of reduced insulin secretion by β-cells without changes in islet insulin content and β-cell mass. Therefore, this suggests that the existence of a liver–β-cell axis depends on normal liver glucose metabolism and correct glucose-dependent regulation of gene expression.

Microarray analysis of liver gene expression showed that in addition to an altered regulation of glycolytic and lipogenic gene expression, there was a coordinated downregulation of most of the cholesterol biosynthesis genes, both in the fasted and re-fed states. This was associated with reduced hepatic cholesterol concentration and bile acid (BA) production. No changes were observed in the expression of Cyp7A1, which codes an enzyme that catalyzes the first committed step in BA production; similar observations were made for other genes regulating the synthesis of BA. These results suggest that a decrease in the production of cholesterol is the primary cause of reduced BAs in feces and plasma. Because the cholesterol biosynthetic pathway was associated with decreased BA levels, the authors propose that BAs might mediate a liver–β-cell axis by maintaining the glucose competence.

Because BAs have recently been proposed to play an important role in the control of glucose homeostasis through TGR5-dependent stimulation of glucagon-like peptide-1 (GLP-1) production, and because GLP-1 can increase β-cell glucose competence, they tested GLP-1 plasma levels in the basal and re-fed states. No differences were found between the control and LG2KO mice, suggesting that GLP-1 secretion does not explain the decreased β-cell glucose competence. In contrast, their data provide support for a direct role of BA action in β-cells through an farnesoid X receptor (FXR)-dependent mechanism, because glucose competence of control islets was clearly increased by prior exposure to chenodeoxycholic acid (CDCA) or the FXR agonist, GW4064; an effect that was suppressed in $FXR^{-/-}$ islets. This is in agreement with observations that BAs increase insulin production and secretion through an FXR-dependent regulation of adenosine triphosphate-sensitive potassium channels[4,5].

Considered together, we believe that BAs might constitute a link between hepatic glucose management as a way to sense glycemic levels, and in the long-term maintenance of the appropriate insulin secretory capacity of the pancreatic β-cells (Figure 1). However, understanding the link between the hepatic glucose sensing mechanism and the control of cholesterol biosynthesis genes will clearly require further investigation. In addition, further studies will be required to fully elucidate the role of BAs on diverse aspects of the control of glucose homeostasis, because BAs form a family of structurally related, but very diverse, molecules that might have widely different biological effects. Finally, because cholesterol is the precursor of other biologically active substances, such as isoprenoid, dolichol or steroids, other cholesterol-derived molecules might also have an impact on β-cell function. Consequently, further research on these processes will provide an alternative basis for the successful treatment of type 2 diabetes mellitus.

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REFERENCES

1. Guillam MT, Burcelin R, Thorens B. Normal hepatic glucose production in the absence of GLUT2 reveals an alternative pathway for glucose release from hepatocytes. *Proc Natl Acad Sci USA* 1998; 95: 12317–12321.
2. Burcelin R, Del Carmen Munoz M, Guillam MT, *et al*. Liver hyperplasia and paradoxical regulation of glycogen metabolism and glucose-sensitive gene expression in GLUT2-null hepatocytes. Further evidence for the existence of a membrane-based glucose release pathway. *J Biol Chem* 2000; 275: 10930–10936.
3. Seyer P, Vallois D, Poitry-Yamate C, *et al*. Hepatic glucose sensing is required to preserve beta cell glucose competence. *J Clin Invest* 2013; 123: 1662–1676.
4. Popescu IR, Helleboid-Chapman A, Lucas A, *et al*. The nuclear receptor FXR is expressed in pancreatic beta-cells and protects human islets from lipotoxicity. *FEBS Lett* 2010; 584: 2845–2851.
5. Dufer M, Horth K, Wagner R, *et al*. Bile acids acutely stimulate insulin secretion of mouse β-cells via farnesoid X receptor activation and K (ATP) channel inhibition. *Diabetes* 2012; 61: 1479–1489.

Doi: 10.1111/jdi.12199